Summary of the Clinical Studies Reported in the Annual Scientific Sessions of the American Heart Association (Chicago, USA, November 12-15, 2006)

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A group of clinical trials were selected for presentation in special sessions in the American Heart Association 2006 scientific sessions. These studies were chosen for their special relevance and their results communicated orally. Summaries of the reports have been published online. The endpoints, methods, and results of these studies are briefly described based on what was presented. As the results of most of these studies have not yet been published as original articles, the information offered in the current article should be understood as being preliminary.

PRIMARY AND SECONDARY PREVENTION

MEDAL Trial (Multinational Etoricoxib and Diclofenac Arthritis Long-Term Study Program). Cardiovascular Risk After Long-Term Treatment With Etoricoxib versus Diclofenac in Patients With Osteoarthritis and Rheumatoid Arthritis

Presented by Christopher P. Cannon, Boston, USA

Introduction and endpoints. The cardiovascular safety of conventional non-steroid antiinflammatory agents (NSAIDs) and cyclo-oxygenase-2 (Cox-2) selective inhibitors is a subject of great clinical importance. The present study was based on the hypothesis that the risk of thrombotic cardiovascular events in patients with arthritis receiving treatment with etoricoxib is not lower than that associated with diclofenac treatment.

Methods. The MEDAL program consisted of three double-blind randomized studies in patients with osteoarthritis (n=24 913) or rheumatoid arthritis (n=9789), assigned to etoricoxib (60 or 90 mg daily) or diclofenac (150 mg daily). The primary endpoint was the appearance of thrombotic cardiovascular events, confirmed by a blinded adjudicating committee. Non-inferiority of treatment was defined as an upper 95% CI bound of the hazard ratio<1.30.

Results. Mean duration of treatment was 18 (12) days. In total, 320 patients in the etoricoxib group and 323 in the diclofenac group presented thrombotic cardiovascular events, translating into incidence rates of 1.24 and 1.30 per 100 patient-years with a hazard ratio of 0.95 (95% CI, 0.81-1.11) for etoricoxib compared to diclofenac. The incidence of upper gastrointestinal tract events (perforation, bleeding, obstruction, or ulcer) was lower with etoricoxib than with diclofenac (0.67 vs 0.97 per 100 patients/year; hazard ratio=0.69 [0.57-0.83]), whereas the rates of complicated gastrointestinal events were similar for both drugs.

Conclusions. The incidence of thrombotic cardiovascular events in patients with arthritis taking etoricoxib is similar to that of patients taking diclofenac, when both drugs are administered long-term.

This study has already been published as a complete article.[1]

Effect of Pioglitazone Compared to Glimepiride on Carotid Intima-Media Thickness in Patients With Type 2 Diabetes. Results of the CHICAGO Study

Presented by Theodore Mazzone, Chicago, USA

Introduction and endpoints. Carotid intima-media thickness (CIMT) is a marker for coronary atherosclerosis which independently predicts cardiovascular events. Their incidence increases in patients with type 2 diabetes mellitus (DM2). Short-term studies have shown that thiazolidinediones, such as pioglitazone, can reduce progression of CIMT in patients with diabetes. However, the results of long-

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term studies are contradictory. The present study was designed to evaluate the effect of pioglitazone versus glimepiride on changes in CIMT in the common carotid artery in patients with DM2.

Methods. A randomized, double-blind, comparator-controlled, multicenter study on patients with DM2, run in 28 clinical centers in the Chicago metropolitan area (highly multiracial and multi-ethnic), from October 2004 to May 2006. The treatment period was 72 weeks, with 1-week follow-up. Carotid intima-media thickness images were acquired by a single operator at one center and measured by a single interpreter blinded to the treatment patients received. Automated edge-detection technology was employed. Some 462 adults participated (mean age, 60 [8] years; mean Body Mass Index, 32 [5.1]) with DM2 (mean duration, 7.7 [7.2] years, glycosylated hemoglobin, 7.4 [1%]), recently diagnosed or treated at the time of inclusion with diet and exercise, a sufonylurea, metformin, insulin or a combination of these drugs. The patients received pioglitazone (15-45 mg/day) or glimepiride (1-4 mg/day). The primary endpoint was the absolute change (inclusion at the end of the study) in posterior-wall CIMT in both common carotid arteries.

Results. The mean change in CIMT was less in the pioglitazone group versus the glimepiride group at each time point (weeks 24, 48, and 72). At the end of the study, the primary endpoint of progression was less in patients receiving pioglitazone than in those receiving glimepiride (–0.0001 vs 0.012 mm, respectively; difference,–0.013 mm; 95% CI, –0.042 to –0.006; *P*=.008). The beneficial effect of pioglitazone on CIMT was similar in all the prespecified groups based on age, sex, systolic blood pressure, DM duration, Body Mass Index, glycosylated hemoglobin value, and stain use.

Conclusions. After an 18-month treatment period in patients with DM2, pioglitazone slowed CIMT progression compared to glimepiride.

This study has already been published as a complete article.[2]

Randomized Study on the Use of Folic Acid and B-Group Vitamins in the Secondary Prevention of Cardiovascular Events in Women: Results of the WAFACS Study (Women's Antioxidant and Folic Acid Cardiovascular Study)

Presented by Christine M. Albert, Boston, USA

Introduction and endpoints. Recent randomized studies of secondary prevention have failed to demonstrate that folic acid combined with B vitamins have a beneficial effect on cardiovascular risk. However, few women participated in these studies and there are questions concerning whether the introduction of folic acid fortification into the control group's diet could have contributed to the absence of positive results in the previous studies. The WAFACS study tested the combination of folic acid (2.5 mg daily), vitamin B_6 (50 mg daily), and vitamin B_{12} (1 mg daily) compared to placebo for the primary composite endpoint of myocardial infarction, stroke, revascularization, or cardiovascular death in women at high risk of cardiovascular disease.

Methods. Some 5442 female health professionals participated in a randomized study on the usefulness of antioxidant vitamins and were randomized to receive a combination of folic acid+vitamin B_6+vitamin B_{12} or placebo. The participants were >40 years old, with a previous history of cardiovascular disease, or had 3 or more cardiovascular risk factors. Follow-up was carried out over a mean of 7.3 years. In a substudy of 300 women, blood samples were analyzed which had been compiled between 1993 and 1995 (before beginning the administration of folic acid in 1997), as well as at the end of the study in 2005; these were studied for folic acid and homocysteine concentrations.

Results. During follow-up, 805 women presented a cardiovascular event, including 139 myocardial infarctions, 148 strokes, 508 coronary revascularizations, and 200 cardiac deaths. No effect of folic acid/vitamin B_6/vitamin B_{12} was found in the primary composite endpoint (relative risk [RR]=1.04; 95% CI, 0.91-1.19; *P*=.58). There were no significant differences among any of the individual events, such as myocardial infarction (RR=0.87; 95% CI, 0.63-1.22; *P*=0.42), stroke (RR=1.14; 95% CI, 0.82-1.57; *P*=0.44), revascularization (RR=0.99; 95% CI, 0.83-1.17; *P*=0.87) and cardiovascular death (RR=1.03; 95% CI, 0.78-1.36; *P*=0.82). It was found that the treatment significantly reduced homocysteine concentrations in the active treatment subgroup (median, 10.0 vs 12.3; *P*<.001). Concentrations of folic acid increased in the placebo group (from 9.0 to 16.4; *P*<.001) due to the effect of the progressive increase in folic acid fortification in the diet. However, this did not lead to reduced homocysteine concentrations.

Conclusion. No beneficial effect was found of combining folic acid+vitamin B_6+vitamin B_{12} on cardiovascular risk in women at high risk of heart disease, despite significant reductions in homocysteine concentrations being achieved. This lack of effectiveness does not seem to be explained by the folic acid fortification in the diet.

WACS Study (Women's Antioxidant Cardiovascular Study). Randomized Factorial Study on the Vitamins C, E, and Betacarotene in the Secondary Prevention of Cardiovascular Events in Women

Presented by Nancy R. Cook, Boston, USA

Introduction and endpoints. Randomized studies have failed to demonstrate that antioxidant vitamins have an effect on cardiovascular disease, either when administered in isolation or as a vitamin "cocktail." However, only a few studies have analyzed the interaction of antioxidants in isolation and no previous study has analyzed the potential effect of vitamin C on cardiovascular risk. The aim of the WACS study was to test, in a factorial design, if vitamins C (500 mg day), E (600 U every 48 h) or betacarotene (50 mg every 48 h) had an effect on the combined endpoint of myocardial infarction, stroke, revascularization, or cardiovascular death in women with a high cardiovascular risk.

Methods. Some 8171 female health professionals were randomized to receive vitamin C, vitamin E, and/or betacarotene as placebo or active drug in a 2×2×2 factorial design. The participants were >40 years old, with a history of cardiovascular disease, or three or more classical risk factors. Follow-up was carried out over mean of 9.4 years.

Results. In total, 1464 women presented an episode included in the primary endpoint, with 274 myocardial infarctions, 298 strokes, 889 coronary revascularizations, and 409 cardiovascular deaths. No effect was found for vitamin C (RR=1.01; 95% CI, 0.91-1.12; *P*=.79), vitamin E (RR=0.94; 95% CI, 0.85-1.04; *P*=.23) or betacarotene (RR=1.01; 95% CI, 0.91-1.12; *P*=.83) on the primary composite endpoint. Furthermore, neither was any significant effect demonstrated on the individual secondary endpoints of myocardial infarction, stroke, revascularization, or cardiovascular mortality. In the subgroup analysis, unlike women with previous cardiovascular disease, women with three or more risk factors had fewer strokes when administered vitamin C (RR=0.58; 95% CI, 0.35-0.97; *P*=.04) versus placebo. The same effect on the incidence of stroke was found in active smokers (RR=0.52; 95% CI, 0.29-0.91; *P*=.02). Significant reductions in the primary endpoint were found with vitamin E (RR=0.88; 95% CI, 0.79-0.99; *P*=.03) and less incidence of myocardial infarction (RR=0.77; 95% CI, 0.58-1.02; *P*=.07) in women with a history of cardiovascular disease. No significant effects were found in any subgroup treated with betacarotene. Neither were significant interactions found among the antioxidant agents for the primary endpoint; however, the women randomized to receive active vitamin C and E treatment had a lower incidence of stroke (*P*=.03).

Conclusions. In women with a high risk of cardiovascular disease no beneficial effects were found on the cardiovascular composite endpoint of the administration of vitamin C, vitamin E, or betacarotene. These findings in the subgroups could be due to chance, but deserve further research.

FAME Trial (The Federal Study of Adherence to Medication in the Elderly). Randomized Controlled Study on the Impact of a Program of Adherence to Treatment for Controlling Lipids and Blood Pressure

Presented by Jeannie K. Lee, Washington DC, USA

Introduction and endpoints. Elderly patients with coronary risk factors often require multiple medication treatment involving increased chances of dropout. Failure to adhere to treatment, which is very common and difficult to solve, reduces the health benefits of multiple medication use. Thus, effective strategies are needed aimed at increasing adhesion to treatment in elderly patients; benefits have still to be demonstrated regarding prognosis for these types of measures.

Methods. The study included patients ≥65 years old, selected from the group taking more than four chronic medications a day. After a 2-month run-in phase, where adhesion to treatment (through counting medications), blood pressure, and low-density lipoprotein cholesterol (LDL-C) was recorded, the patients were entered into a 6-month intervention phase consisting of standardized medication use, education by a clinical pharmacologist and medications dispensed in blister packs of each patient's daily dose. The study's primary endpoints were changes in adherence to treatment and modifications in LDL-C and blood pressure. After this phase, patients were randomized to continue with the intervention for another 6 months with the blister packs or to usual treatment (in bottles), with the same primary endpoint.

Results. Some 200 patients (77.5% male; age, 79 [6] years) were included taking a mean of 9 (3) drugs. Risk factors were hypertension in 92% and hyperlipidemia in 81%. Medication adherence was 61.3 (13.6%). At 6 months, adhesion to treatment increased to 96.7 (7.1%) (*P*<.001) and was associated with significant reductions in systolic blood pressure (132.7 [14.6] vs 129.0 [16.0] mm Hg; *P*<.005) and LDL-C (94.1 [25.9] vs 89.9 [24.8] mg/dL; *P*<.003). The findings of the later randomized study showed that, in the usual treatment group, adhesion to treatment decreased to 69.1%, whereas in the intervention group it remained at 95.5% (*P*<.001). Reductions in systolic blood pressure in treated hypertensive patients was greater in the intervention group than in the usual treatment group (–6.9 vs –1.0

mm Hg; *P*=.04). Among the treated hyperlipidemic patients, the reduction in LDL-C was not significantly different between the two groups.

Conclusions. In elderly patients with a high risk of lack of adherence to treatment, receiving multiple medications for cardiovascular risk factors, a complete pharmacy care program including education, and personalized single-dose packs increases adhesion to treatment by more than 50%, leading to clinically important reductions in blood pressure and LDL-C figures.

SLx-4090: First Experience in Humans and Demonstration of Mechanism of Action of an Enterocyte-Specific Microsomal Triglyceride Transfer Protein Inhibitor

Presented by William T. Prince, Neuss, Germany

Introduction and endpoints. Microsomal triglyceride transfer protein (MTP) facilitates the formation and transfer of chylomicron from the liver and intestine. Previous studies with MTP inhibitors have caused fatty degeneration of the liver and led to premature closure of their clinical development before or during phase 2A studies. SLx-4090 is a small molecule that acts as a potent MTP inhibitor designed to only act on enterocytes and is not absorbed systemically, thus avoiding hepatotoxicity. This study was the first trial in humans designed to analyze its safety, tolerability, and efficacy in relation to postprandial triglyceride values.

Methods. A single-center, randomized, double-blind, placebo-controlled study. Three cohorts of 8 healthy volunteers each receiving 3 different single doses (5, 10, and 50 mg; 100, 200, and 300 mg; 400, 600, and 800 mg) of SLx4090 or placebo. The volunteers were studied for 24 h after administration and the primary endpoints were safety and tolerability. The secondary endpoints were postprandial triglyceride concentrations. In cohorts 1 and 2, SLx-4090 was followed by food 4 h after the dose, but in cohort 3, SLx-4090 was administered immediately before breakfast.

Results. Individual doses of SLx-4090 were well tolerated. No adverse effect was seen. Furthermore, SLx-4090 was not detected in plasma samples at any dose level. Minimum quantities of an inactive metabolite of the drug were occasionally detected at 5 and 12 h following dosing in some subjects who received the 400, 600, and 800 mg dose. After the individual 400, 600, and 800 mg doses, the mean postprandial maximum increase over baseline triglyceride values was half the increase seen in subjects receiving placebo. The difference was significant at 5, 6, and 7 h after dosing (*P*<.05) for the 3 doses, and significant at 4 h for 600 and 800 mg doses.

Conclusion. Individual doses of SLx-4090 inhibit MTP in intestinal enterocytes and reduce postprandial triglyceride concentrations, without systemic exposure to the drug. SLx-4090 proved to be safe and well-tolerated, and is already in the next phase of clinical development.

ISCHEMIC HEART DISEASE

First-in-Human Experience of an Antidote-Controlled Anticoagulant Using RNA Aptamer Technology: Results of the Phase IA Evaluation of the REG1 Anticoagulation System, a Product for Controlled Regulation of Factor IXa

Presented by Christopher Dyke, Durham, USA

Introduction and endpoints. It is accepted that anticoagulant drugs should be effective, durable, have rapid onset and be reversible to guarantee patient safety. The present work studied the effect in volunteers of a new anticoagulation system (REG1) developed through using a protein oligonucleotide that binds factor IXa, as well as its complementary oligonucleotide (antidote). The primary endpoint was to study the safety profile and characterize the pharmacokinetic (PK) and pharmacodynamic (PD) response in this first trial in humans.

Methods. A single-blind, dose-escalation, placebo-controlled study including 85 patients randomized to receive drug bolus or placebo, followed 3 h later by antidote bolus or placebo. Samples were taken to study PK and PD response.

Results. Mean age was 32 years, 34% of the patients were female and mean weight was 79 kg. No changes were found in the results of median hemoglobin, platelet, creatinine, or liver function tests. Neither were adverse effects found in relation to bleeding or other side effects related to the drug. A predictable dose-response effect was seen on the activated partial thromboplastin time (aPTT) after administration of drug bolus, as well as a rapid and sustained return of baseline aPTT values after administration of the antidote. Activated coagulation time (ACT) followed the same behavior as aPTT whereas no changes were seen in prothrombin time, as expected.

Conclusion. These results represent the first-in-human experience of a new compound. No adverse effects were seen and aPTT had an excellent dose-response relationship. Administering the antidote led to the rapid and sustained return of aPTT to baseline values. These results contribute to the development of a new platform of tailored anticoagulant drugs to use in patients with thrombotic diseases of the arterial and venous cardiovascular systems.

INTERVENTIONIST/SURGICAL CARDIOLOGY

APEX AMI Trial (Assessment of Pexelizumab in Acute Myocardial Infarction): Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial on Pexelizumab in Patients With Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention

Presented by Paul W. Armstrong, Edmonton, Canada

Introduction and endpoints. The principal endpoint of the study was to determine if treatment with pexelizumab (a C5 complement inhibitor) reduces all-cause mortality at 30 days in patients with acute myocardial infarction with elevation of the ST segment treated with primary angioplasty. The secondary endpoints were to determine if the drug could reduce mortality at 90 days and a combined endpoint of death, cardiogenic shock, or congestive heart failure at 30 days.

Methods. A phase-3 multicenter, randomized, double-blind, parallel-group, placebo-controlled trial of pexelizumab use, and primary PCI. Patients were stratified according to location of the infarction (high risk, inferior, or other location) and randomized to receive active treatment or placebo. The study included 5745 patients, the last in May 2006. The patients received 2 mg/kg intravenous bolus pexelizumab or placebo over 10 min followed, as soon as possible, by 0.05 mg/kg/h pexelizumab or placebo infusion over the following 24 h.

Results. The proportion of inferior myocardial infarction was 41%; 16% of the patients were diabetic and 46% were smokers. The median time from symptom onset to beginning primary PCI was 3.3 h, and mean time from beginning bolus treatment to beginning the procedure was approximately 0.25 h. Stents were used in 89% of the patients and glycoprotein IIb/IIIa inhibitors in 69%. The study was stopped prematurely. No differences were seen in the primary endpoint of 30-day mortality (4.1% vs 3.9% pexelizumab vs placebo group, respectively; hazard ratio [HR]=1.04; *P*=.78). Neither were differences seen in the secondary composite endpoint at 30 days (9.0% vs 9.2%; HR = 0.98; *P*=.82). Cardiovascular events at 90 days did not differ between the two groups, including mortality (4.9% vs 4.5%), congestive heart failure (4.8% in the two groups), shock (3.4% vs 3.5%) and reinfarction (3.0% vs 2.4%) for pexelizumab versus placebo, respectively. Sepsis at 14 days, which was a rare event, tended to be slightly less frequent in the pexelizumab group (0.56 vs 0.90%; HR=0.62; *P*=.13).

Conclusions. The administration of pexelizumab was not associated with a difference in 30-day mortality compared to placebo in the patients with acute ST-segment elevation myocardial infarction treated with primary PCI.

J-WIND Trial (Japan Working Groups on Acute Myocardial Infarction for the Reduction of Necrotic Damage by Atrial Natriuretic Peptide or Nicorandil). A Large-Scale Study on the Effect of Atrial Natriuretic Peptide or Nicorandil as an Adjunct Therapy to Percutaneous Coronary Intervention in Treating ST-Segment Elevation Acute Myocardial Infarction

Presented by Masafumi Kitakaze, Suita, Japan

Introduction and endpoints. Despite the demonstrated benefits of early reperfusion, heart failure, and cardiovascular mortality continue to be frequent following acute myocardial infarction (AMI). Reducing the size of the infarction could decrease these long-term risks. The aim of this study was to evaluate the efficacy of nicorandil and human atrial peptide natriuretic (ANP) (carperitide) on the size of the infarction and on subsequent cardiovascular prognosis.

Methods. Two independent, prospective, single-blind, randomized trials were run in 94 hospitals in Japan. Patients were treated with a reperfusion strategy after AMI and randomized to receive nicorandil (0.067 mg/kg bolus and afterwards 1.67 μg/kg/min for 24 h continuous infusion) or carperitide (0.025 μg/kg/min continuous infusion for 3 days) or equivalent doses of placebo. Mean follow-up time was 2.5 years. The primary endpoints were size of the infarction (estimated by the area under the curve of creatine kinase isoenzyme MB [CK-MB]) and ejection fraction evaluated via left ventriculography. The incidence of cardiovascular mortality, cardiovascular events, or heart failure were defined as secondary endpoints. In total, 613 subjects received treatment with nicorandil (n=309) or placebo (n=304) and 603 patients received carperitide (n=209) or placebo (n=313).

Results. The mean size of the infarction was significantly reduced by carperitide (14.7% reduction vs control; *P*=.016), but no differences were seen between the nicorandil group versus control group. Furthermore, carperitide was effective in achieving a greater improvement in ejection fraction (5.1%), which was not seen with nicorandil administration. The results were similar in the prespecified subgroups. Regarding secondary endpoints, a 25.9% reduction in reperfusion injury was seen in the carperitide group compared to the control group; no reduction was seen with nicorandil. Neither were differences seen in mortality or the composite endpoint between the active treatment and control groups. No differences were seen in mortality or the composite endpoint between the active treatment and control groups in any of the trials. The composite endpoint of cardiac death or heart failure was less frequent in the carperitide group than in the control group (hazard ratio [HR]=0.27; *P*=.011), but no differences were seen with nicorandil.

Conclusions. In the patients with treated ST-segment elevation AMI and primary PCI, the administration of human ANP (carperitide) is associated with a reduction in infarction size and greater ejection fraction versus the control group. Treatment with nicorandil was not associated with differences in infarction size or in ejection fraction versus the control group. Furthermore, a 70% reduction was seen in the incidence of cardiac death or heart failure in the carperitide group versus control group. However, the size of the trial was small and large-scale studies are needed to confirm these results regarding clinical events.

MAGIC Trial (Myoblast Autologous Grafting in Ischemic Cardiomyopathy). First Randomized, Placebo-Controlled Trial on the Usefulness of Autologous Myoblasts in Patients With Ischemic Cardiomyopathy

Presented by Philippe Menasché, Paris, France

Introduction and endpoints. Several phase 1 and 2 trials have demonstrated the safety of transplanting autologous myoblasts from the skeletal muscle into postinfarction lesion areas while also demonstrating a potential risk of arrhythmias. However, due to their design, these trials have not been able to clearly demonstrate a causal relationship between the arrhythmias and myoblast injection, or provide clear evidence of their functional efficacy. With the aim of clarifying these aspects, the MAGIC trial was designed to study the safety and efficacy of 2 doses of skeletal myoblasts as compared to placebo, in the treatment of ischemic cardiomyopathy.

Methods. The study included 97 patients in 24 centers in Europe. To be included, the Patients had to have presented a previous infarction treated with coronary artery bypass graft surgery using venous and arterial to be included. The patients had to fulfill the following three major selection criteria: left ventricular dysfunction, defined as ejection fraction ≤35%, a history of acute myocardial infarction with at least 2 contiguous akinetic segments which were unviable as demonstrated by dobutamine stress test, and an indication for coronary bypass. The 97 patients were randomized into three groups. The high-dose group (30 patients) received a direct injection of myoblasts into the infarct and adjacent area, of around 800 million cells via 30 injections. The low-dose group (33 patients) received a direct injection of around 400 million myoblasts. The third group (34 patients) received an injection of the suspension medium without active cells. All patients received an implantable cardioverter defibrillator (ICD).

Results. The study was stopped prematurely when an independent clinical endpoint committee indicated that it was unlikely that the treatment was superior to placebo regarding the primary endpoint: functional recovery in regional wall motion or global systolic function assessed by ejection fraction via echocardiography. No significant differences were found in any of these endpoints. No differences were seen between groups in the incidence of major adverse cardiac events or ventricular arrhythmias. Although the results were negative in showing increases in ejection fraction or improvements in regional wall motion, there was a reduction in ventricular volume (from 12% to 13% regarding baseline values) in patients receiving high doses of cells compared to the placebo group. Furthermore, in the subgroup of 48 patients where ejection fraction was measured by nuclear angiography, an increase in ejection fraction was seen in the high-dose group compared to control group.

Conclusions. Although no beneficial effect on ejection fraction or regional wall motion assessed by angiography was found, injecting high doses of myoblasts during coronary artery bypass graft surgery could have a beneficial effect on left ventricular volumes. Large-scale studies are needed to confirm these findings. In addition, the study has planned a total 1-year follow-up.

OAT Study (Occluded Artery Trial)

Presented by Judith S. Hochman, New York, USA

Introduction and endpoints. It is unknown if stable high-risk patients presenting total occlusion of the infarct-related artery (IRA) — identified after the accepted period for myocardial reperfusion in the acute phase of acute myocardial infarction (AMI) has passed — should be treated with percutaneous coronary intervention (PCI) plus optimal medical treatment, with the aim of reducing later complications.

Methods. A randomized study including 2166 stable patients presenting total occlusion of the IRA 3 and 28 days post-AMI, with at least one risk factor (ejection fraction <50% or proximal artery occlusion). Of these patients, 1082 were assigned to the PCI plus stenting and optimal medical treatment arm, and 1084 to optimal medical treatment alone. The primary endpoint was the composite of death, re-AMI or New York Heart Association (NYHA) class IV heart failure.

Results. The cumulative event rate at 4 years was 17.2% in the PCI arm and 15.6% in the medical treatment arm (the risk ratio for death, reinfarction or heart failure in the PCI arm vs medical treatment was 1.16; 95% confidence interval [CI], 0.92-1.45; *P*=.20. The rates of re-AMI (fatal or non-fatal) were 7.0% and 5.3%,

respectively (risk ratio=1.36; 95% CI, 0.92-2.0; *P*=.13). Non-fatal infarction rates were 6.9% and 5%, respectively (risk ratio=1.44; 95% CI, 0.96-2.16; *P*=.08); only 6 re-AMI (0.6%) were associated with the assigned PCI procedure. NYHA class IV heart failure (4.4% vs 4.5%) and death (9.1% vs 9.4%) rates were similar. No interactions were seen between treatment effect and subgroups defined by variables such as age, sex, race, or ethnic group, IRA, ejection fraction, diabetes, Killip class and time between infarction, and randomization.

Conclusions. Percutaneous coronary intervention on total occlusions of the IRA 3 to 28 days after AMI in stable high-risk patients did not reduce the incidence of death, reinfarction or heart failure; there was a trend toward excess non-fatal re-AMI during 4-year follow-up.

This study has been published as a complete article.[3]

TOSCA-2 Study (Total Occlusion Study of Canada-2)

Presented by Vladimir Dzavik, Toronto, Canada

Introduction and endpoints. The aim of this OAT trial substudy was to determine if opening a persistently occluded artery after acute myocardial infarction (AMI) by percutaneous coronary intervention (PCI) in patients beyond the acute phase of AMI increases artery patency and indexes of left ventricle size and function in the long-term.

Methods. From May 2000 to July 2005, 381 patients with occlusion of the IRA 3-28 days after AMI (median, 10 days) were randomized to receive PCI with stenting or optimal medical treatment only. Coronary and left ventricle angiography were repeated at 1 year following randomization (n=332; 87%). Primary endpoints of the substudy were IRA patency and the change in ejection fraction. Secondary endpoints included changes in left ventricular end-systolic and end-diastolic volume indexes, and wall motion.

Results. Percutaneous coronary intervention was successful in 92% of cases. One year later, 83% of patients in the PCI arm versus 25% of patients in the medical treatment arm had patent IRA (*P*<.001). Ejection fraction increased significantly in both groups (*P*<.001), with no differences between them (PCI arm, 4.2 [8.9], n=150 vs medical treatment arm, 3.5 [8.2], n=136; *P*=.47). The median change and interquartile range in the left ventricular end-systolic volume index were -0.5 (–9.3 to 5.0) versus 1.0 (–5.7 to 7.3) mL/m^2 (*P*=.10), whereas the median change in left ventricular end-diastolic volume was 3.25 (–8.2 to 13.3) versus 5.3 (–4.6 to 23.2) mL/m^2, *P*=.07 in the PCI arm (n=86) versus medical treatment arm (n=76), respectively.

Conclusions. Percutaneous coronary intervention with stenting in the IRA in the subacute phase was effective in maintaining long-term patency, but did not have an effect on ejection fraction. Based on these results and the absence of clinical benefit in the OAT trial, the systematic practice of PCI is not recommended in patients with persistent occlusion of the IRA.

This study has been published as a complete article.[4]

PACCOCATH ISR Trial (Treatment of in-Stent Restenosis by Paclitaxel-Coated PTCA Balloons)

Presented by Dr Bruno Scheller, Saar, Germany

Introduction and endpoints. The treatment of coronary in-stent restenosis is hindered by the high incidence of recurrent in-stent restenosis. The efficacy and safety of a paclitaxel-coated balloon were evaluated in a population with restenosis due to previous stenting by comparing this device with conventional balloon.

Methods. The study included 52 patients with in-stent restenosis in a randomized, double-blind, multicenter trial comparing the effects of a paclitaxel-coated balloon catheter (3 µg/mm^2 of the balloon surface area) with those of an uncoated balloon catheter in coronary angioplasty. The primary endpoint for measurement was late luminal loss as measured by quantitative angiography. The secondary endpoints were restenosis rates (binary variable) and major adverse cardiac events.

Results. Some 80% of the patients in both arms presented multivessel disease. No significant differences were seen in baseline measurements with quantitative angiography. At 6 months, arteriography showed that mean in-segment late luminal loss was 0.74 (0.86) mm in the patients with standard balloon catheters versus 0.03 (0.48) mm in the coated-balloon group (*P*=.002). Ten of the 23 patients (43%) in the uncoated-balloon group presented restenosis, compared to 1 of the 22 patients (5%) in the paclitaxel-coated balloon group (*P*=.002). At 12 months, the major adverse cardiac event rate was 31% in the uncoated-balloon group and 4% in patients in the coated-balloon group (*P*=.01). This difference was basically due to the need for revascularization of the target lesion in six patients in the standard balloon group (*P*=.02).

Conclusion. The treatment of coronary in-stent restenosis with paclitaxel-coated balloon catheters significantly reduced the incidence of restenosis. These data seem to indicate that stenting and sustained drug release may not be necessary at the lesion site to inhibit restenosis through local drug delivery.

This study has been published in the form of a complete article.[5]

ARRHYTHMIA

PABA-CHF Study. Randomized Controlled Trial of Pulmonary Vein Antrum Isolation Versus Atrioventricular Node Ablation and Bi-Ventricular Pacing in Patients With Congestive Heart Failure

Presented by Andrea Natale, Cleveland, USA

Introduction and endpoints. Pulmonary vein antrum isolation (PVI) is a percutaneous radiofrequency technique increasingly used for treating atrial fibrillation. atrioventricular node ablation (AVNA) followed by biventricular pacemaker (AVNA-BVP) implantation has proven superior to standard pacemaker implantation with right ventricular pacing for treating atrial fibrillation.

Methods. A randomized, prospective, multicenter study in patients presenting symptomatic atrial fibrillation, resistant to drug treatment, with ejection fraction ≤40% and NYHA functional class I-III. The patients were randomized to receive PVI or AVNA-BVP; patients in the PVI group with persistent atrial fibrillation at 3 months underwent another PVI. All patients completed the Minnesota Living with Heart Failure (MLWHF) questionnaire and a 6-min walk test. There was 6-month follow-up with monitoring for symptomatic and asymptomatic episodes of recurrent atrial fibrillation.

Results. Some 35 patients underwent PVI and 36 AVNA-BVP, with no-one lost at 6-month follow-up. There were no baseline differences between the 2 groups. The study reached its primary endpoints in favor of PVI treatment vs AVNA-BVP in relation to MLWHF scores at 6 months (61 vs 79; *P*<.0001). Furthermore, distances covered at 6 min were also superior (345 vs 301 m; *P*=.0002) as well as ejection fraction (35% vs 29%; *P*<.0001). Improvements were also seen in persistent and permanent paroxysmal atrial fibrillation in the PVI group versus the AVNA-BPV (94% vs 6%; *P*<.0001). The size of the atrium in the PVI group was less than in the ANAV-BPV group (4.5 vs 4.8 cm; *P*=.003). No complications (including pulmonary vein stenosis) were seen in any of the 2 groups, and the incidence of minor complications was also similar in both groups.

Conclusions. In patients with heart failure presenting atrial fibrillation, PVI produces greater reductions in AF as well as improvements in quality of life compared to ANAV-BPV as shown by the results of the 6-min walk test and echocardiographic parameters; pacemaker dependency is avoided. This study supports the use of PVI in patients with heart failure with drug-resistant atrial fibrillation.

ABCD Trial (Alternans Before Cardioverter Defibrillator)

Presented by Ottaviano Costantini, Cleveland, USA

Introduction and endpoints. Although automatic implantable cardioverter defibrillators (ICD) have proven effective in preventing mortality due to serious ventricular arrhythmias, selection criteria for candidates to receive this high-cost treatment are still imprecise. In fact, a high percentage of the patients currently treated with ICD never present arrhythmic events. The aim of this study was to compare the capacity of two strategies to predict ventricular tachycardia in patients with ischemic cardiomyopathy: in the first strategy, patient treatment was guided by a microvolt T wave alternans (MTWA) test and in the second, by electrophysiologic study (EPS) in the comparison group.

Method. The study included patients with ischemic cardiomyopathy, ejection fraction ≤40%, and documented unsustained ventricular tachycardia. All patients underwent MTWA test and EPS at an interval of no less than 28 days. An ICD was implanted in patients with a positive result (indicating risk of ventricular arrhythmias) in either of the 2 tests. In the patients where both tests were negative, ICD implantation was recommended but not compulsory. In the patients with indeterminate results in the MTWA test and positive ones in EPS, the result was considered positive.

Results. The study included 566 patients with a mean baseline ejection fraction of 28%: 51% were in NYHA class II, 30% in class I, and 19% in class III. The EPS was positive in 39% of patients and negative in 61%. The MTWA was positive in 46%, negative in 29% and indeterminate in 25%.

The positive predictive values of both methods were similar (11% for EPS and 9% for MTWA; *P*=NS), as well as the negative predictive values (96% vs 95%, respectively; *P*=NS). The arrhythmic event rate was 7% at 1-year follow-up and 13% at 2 years. The highest rates were found in the groups with positive EPS and MTWA (12.6%) and the lowest in patients with both tests negative (2.3%), whereas the remainder presented intermediate values: 7.5% in the patients with positive EPS and negative MTWA, and 5.0% in those presenting positive MTWA and negative EPS. When the time of onset of events was analyzed, EPS predicted these at 9-month follow-up but not before, whereas MTWA predicted events in the earliest phase, but only up to 12-month follow-up.

Conclusions. In the patients with ischemic cardiomyopathy without a history of sustained ventricular arrhythmias, the use of a non-invasive procedure, such as MTWA, showed a predictive capacity of arrhythmic events similar to that of EPS. The combined information from both tests was higher than either alone; the patients

with positive results in both tests presented the maximum risk, whereas those with negative results in both presented the lowest risk.

HEART FAILURE

IMPROVE-CHF Trial

Presented by Gordon Moe, Toronto, Canada

Introduction and endpoints. The aim of this study was to evaluate the effect on clinical treatment and costs of using N-terminal pro-brain-type natriuretic peptide (NT-proBNP) testing in the patients admitted to an emergency department with dyspnea and suspected decompensated heart failure (DHF).

Methods. Blood samples were taken for NT-proBNP measurement in all patients included in the study, while the emergency department physician made a concurrent clinical diagnosis. Afterwards, the patients were randomized to receive usual care with the acting physician blinded to NT-proBNP values or to NT-proBNP-guided treatment after the values were reported to the physician. The values of NT-proBNP were measured again at 72 h in the patients admitted to hospital.

Results. The study randomized 501 patients; 254 to the usual clinical treatment group and 247 to the treatment group where physicians were aware of NT-proBNP concentrations. Rest dyspnea was presented by 55% of the patients, 37% had a history of heart failure or left ventricular dysfunction, 32% had a history of myocardial infarction, 27% diabetes, 36% chronic obstructive pulmonary disease, and 16% stroke. There was a final diagnosis of decompensated heart failure in 227 patients (45%).

The addition of NT-proBNP values to initial clinical assessment improved accuracy in diagnosing heart failure compared to the clinical diagnosis of the emergency physician (C-statistic, 0.904 vs 0.834; *P*<.001). The use of NT-proBNP values as the only diagnostic criterion yielded a C-statistic of 0.855. The median NT-proBNP value was significantly greater in patients with a final diagnosis of DHF than in those with other diagnoses (3717 vs 340 pg/mL; *P*<.001). The duration of mean stay in the patients randomized to the NT-proBNP-guided treatment group was shorter (median, 5.6 vs 6.3 h; *P*=.038). There was no difference in the percentage of patients hospitalized (57% vs 58%), median hospital stay (6 vs 7 days) or percentage of patients admitted to the intensive care unit (8.5% vs 9.9%) between the patients with NT-proBNP-guided treatment and those receiving usual treatment, respectively. Neither were there differences in mortality at 60 days (5.6% vs 4.4%; *P*=.59).

The median total health cost at 60 days was significantly less in the patients randomized to NT-proBNP-guided treatment (6310 vs 7405 Canadian dollars; *P*=.017). The median cost of the initial emergency department visit, including NT-proBNP-test cost, was no different (2196 Canadian dollars in the NT-proBNP-guided treatment group vs 2387 in the treatment group; *P*=.11).

Conclusions. The study showed that measuring NT-proBNP values in patients presenting dyspnea and suspected DHF at an emergency department was associated with greater accuracy in diagnosing DHF, shorter emergency department stay and a reduction in health care costs at 60 days. No reduction in mortality was seen, nor in the percentage of hospitalizations or duration of hospital stay.

SALT 1 and 2 Trials (Study of Ascending Levels of Tolvaptan in Hyponatremia)

Presented by Dr Robert W. Schrier, Denver, USA

Introduction and endpoints. Hyponatremia (serum sodium concentration <135 mmol/L) is a predictor of mortality in patients with chronic heart failure and cirrhosis. Current treatment for acute or chronic hyponatremia tends to be ineffective and poorly tolerated. This study investigated whether tolvaptan, an orally active vasopressin V_2-receptor antagonist that promotes aquaresis —without loss of electrolytes—could be beneficial in hyponatremia.

Methods. The efficacy of tolvaptan was evaluated in patients with euvolemic or hypervolemic hyponatremia in two multicenter, randomized, double-blind, placebo-controlled trials. Patients were randomized to receive oral placebo (223 patients) or tolvaptan (225) in 15 mg/day doses. The tolvaptan dose was increased to 30 mg/day and subsequently to 60 mg/day if needed, depending on serum sodium concentrations. The two primary endpoints for all patients were variations in the mean daily area under the curve for the serum sodium concentration between baseline and day 4, and variations between baseline and day 30.

Results. Serum sodium concentrations increased more in the tolvaptan- treated group than in the placebo group during the first 4 days (*P*<.001) and after the entire 30 days of treatment (*P*<.001). The situation of patients with mild or marked hyponatremia improved (*P*<.001 for all comparisons). Hyponatremia recurred during the week following suspension of tolvaptan on day 30. The side effects associated with the tolvaptan were thirst, dry mouth and excessive urination. A planned analysis combining the two trials showed significant improvements at day 30 compared to baseline in the tolvaptan-treated group, according to scores on the mental component in the Medical Outcomes Study 12-item Short-Form General Health Survey.

Conclusions. Tolvaptan, a selective oral vasopressin V_2-receptor antagonist, was effective in patients with

euvolemic or hypervolemic hyponatremia in increasing serum sodium concentrations at days 4 and 30.

This study has been published as a complete article.[6]

PERIPHERAL VASCULAR DISEASE

Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of VLTS-934 in Subjects With Intermittent Claudication Secondary to Peripheral Vascular Disease

Presented by Paul M. Grossman, Ann Arbor, USA

Introduction. The poloxamer-188 (VLTS-934) is a nonionic block copolymer surfactant that adheres to hydrophobic surfaces that are generated when there is cell damage. The copolymer restores normal hydration to the cellular surface. A recent study evaluated VLTS934 for treating intermittent claudication compared to gene transfer of Del-1 with poloxamer-188. A surprising effect was that the patients treated with VLTS-934 showed a 34% increase in peak walking time and a 0.048 increase in the ankle-brachial index at 90 days compared to baseline values. The present study hypothesized that VLTS-934 could increase peak walking time compared to control serum saline in patients with severe intermittent claudication due to the peripheral vascular disease.

Methods. Patients with bilateral intermittent claudication due to infrainguinal peripheral vascular disease and a 2-10 min peak walking time were included in the study and randomized (1:1) to receive VLTS-934 (84 mL, equivalent to a total of 420 mg poloxamer 188) or placebo (84 mL saline), administered as 21 2-mL bilateral intramuscular injections into the legs on the same day. In addition to tolerability and safety, the primary efficacy endpoint was change in the peak distance traveled at 90 days after inclusion in the study. The secondary endpoints were changes at 90 days in the ankle-brachial index, total work capacity and Walking Impairment Questionnaire.

Results. A total of 157 patients were included and randomized. Mean age was 65.5 (7.7) years, 76% were male, 85% Caucasian, 38% diabetic, 31% active smokers, and 55% former smokers. The primary endpoint of peak walking time changed from 5.1 (83.2) to 6.2 (3.7) min at 90 days in the active-drug group versus 5.0 (2.2) to 6.1 (3.3) min in the placebo group (P=.06). The ankle-brachial index in the treated group at 90 days changed from 0.65 (0.18) to 0.71 (0.24) and from 0.71 (0.24) to 0.70 (0.2) in the placebo group (P=.08). Similarly, no significant differences were seen in the other secondary endpoints between the treated and the placebo groups. The incidence of serious side effects was similar in both groups.

Conclusions. VLTS-934 did not improve intermittent claudication in patients with peripheral vascular disease compared to administering control serum saline. The uniformity of the results in the two groups seems to indicate a relevant placebo effect in patients with intermittent claudication and peripheral vascular disease.

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